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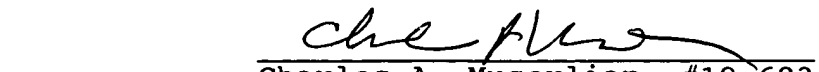
application, to remove multiple dependency from the claims and to conform the claims to the American practice.

Respectfully submitted,
BIERMAN, MUSERLIAN AND LUCAS



Charles A. Muserlian, #19,683
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CAM:sd
Enclosures: Marked-up Version of Specification and Claims
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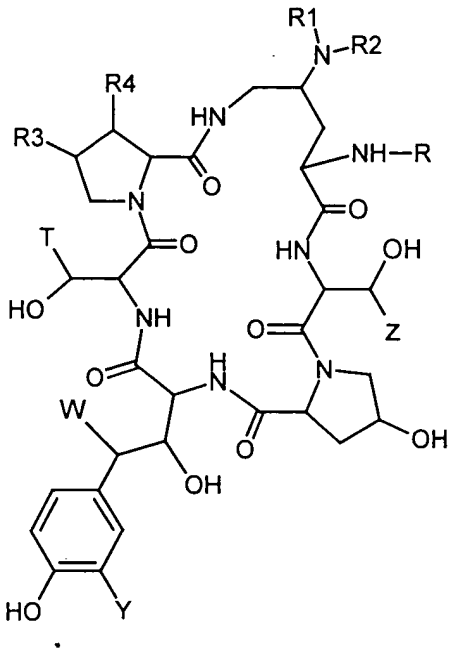
New derivatives of echinocandine, their preparation process and their use as antifungals.

--This application is a 371 of PCT/FR00/01569 filed June 8, 2000.--

The present invention relates to new derivatives of echinocandine, their preparation process and their use as antifungals.

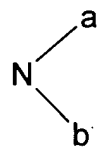
A subject of the invention is in all the possible isomer forms as well as their mixtures, the compounds of formula (I):



(I)

in which

either R_1 and R_2 identical to or different from one another, represent a hydrogen atom, a hydroxyl radical, a linear, branched or cyclic alkyl radical containing up to 8 carbon atoms optionally interrupted by an oxygen atom optionally substituted by a halogen atom, an OH radical, an



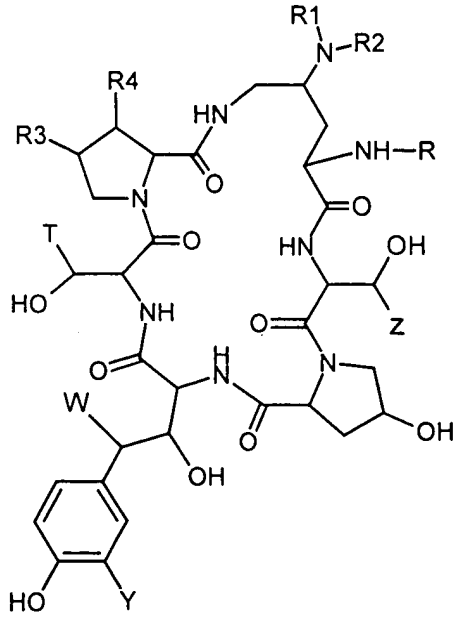
radical, a and b identical to or different from one another, representing a hydrogen atom or an alkyl radical containing up to 8 carbon atoms, a and b can optionally form with the nitrogen atom a heterocycle optionally containing one or more

A compound selected from the group consisting of

MARKED-UP VERSION OF CLAIMS

Our Ref.: 146.1376

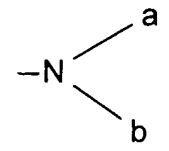
1) ~~In~~ all possible isomeric forms ~~as well as~~ and their mixtures of ~~the~~ compounds of formula ~~(I):~~



(I)

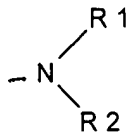
~~in which~~ wherein

either R_1 and R_2 ~~identical to or different from one another, represent a~~ are individually selected from the group consisting of hydrogen ~~atom~~, ~~a~~ hydroxyl ~~radical~~, ~~a linear, branched or cyclic~~ alkyl ~~radical containing~~ of up to 8 carbon atoms optionally interrupted by ~~an~~ oxygen ~~atom~~ and optionally substituted by ~~a~~ halogen ~~atom~~, a member selected from the group consisting of

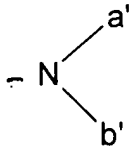
~~an~~ OH ~~radical~~, ~~and an~~  ~~radical~~, a and b

~~identical to or different from one another~~ are individually ~~representing a~~ hydrogen ~~atom~~ or ~~an~~ alkyl ~~radical containing up~~ to 8 carbon atoms, or a and b can optionally form with the nitrogen atom a heterocycle optionally containing at least one ~~or more~~ additional heteroatoms,

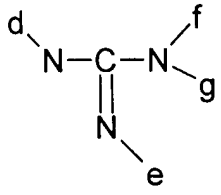
or R_1 forms with the endocyclic carbon atom

carrying ~~the~~  ~~radical~~ a double bond and ~~or~~ R2

~~represents an~~ -XRa ~~radical~~, X ~~representing an~~ oxygen, ~~atom or an~~ -NH- or -N-alkyl ~~radical containing up~~ to 8 carbon atoms and Ra ~~represents a~~ hydrogen ~~atom~~, ~~a linear, branched or~~ cyclic alkyl ~~radical containing~~ up to 8 carbon atoms optionally substituted by ~~or more~~ halogen ~~atoms~~, ~~by one or more~~ -OH, $-CO_2H$, $-CO_2alk$, ~~radicals, by an~~



~~radical~~, a' and b' ~~representing a~~ hydrogen ~~atom, an~~ alkyl ~~radical containing up~~ to 8 carbon atoms, a' and b' can form a heterocycle optionally containing ~~or more~~ additional heteroatoms ~~and~~ or ~~by a~~ heterocycle containing ~~or more~~ heteroatoms or R_2 ~~represents a~~

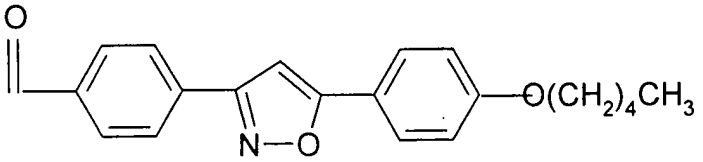


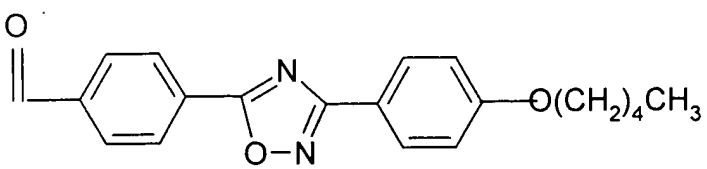
~~radical~~ in which d, e, f and g ~~represent a~~ hydrogen ~~atom~~ or ~~an~~ alkyl ~~radical containing up~~ to 8 carbon atoms, f and g can ~~moreover represent an~~ acyl ~~radical containing~~ up to 8 carbon atoms, and e and f can also form a ring optionally containing ~~or more~~ heteroatoms,

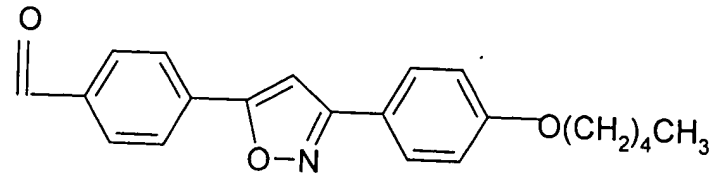
R_3 ~~represents a~~ hydrogen ~~atom~~, ~~a~~ methyl ~~or~~ hydroxyl, ~~radical~~

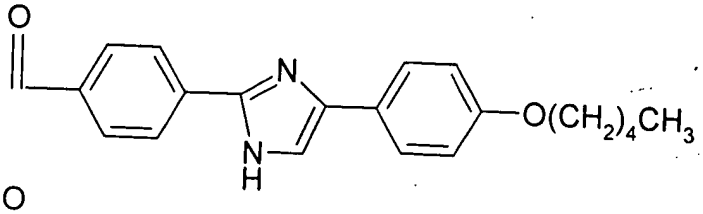
R_4 ~~represents a~~ hydrogen ~~atom~~ or ~~a~~ hydroxyl, ~~radical~~

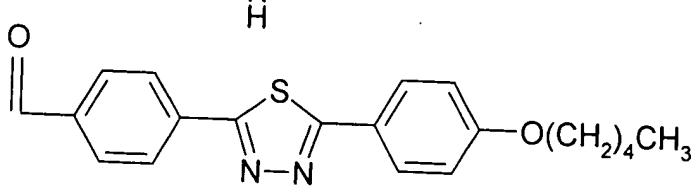
R ~~represents a radical chosen from the following radicals:~~

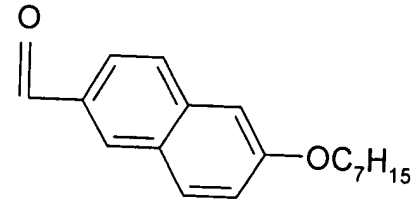


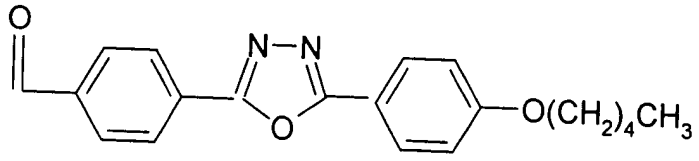


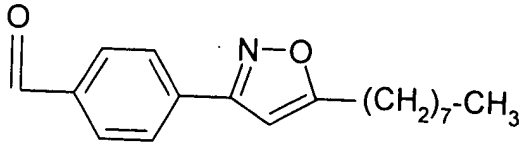


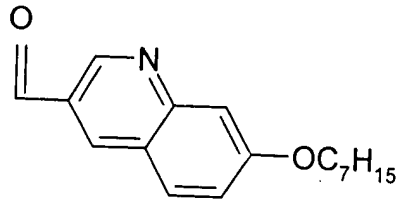




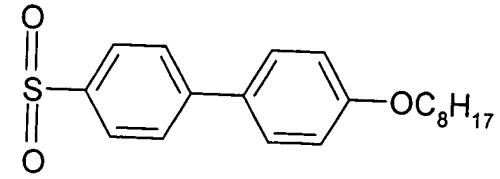








and



T represents a hydrogen atom, a methyl radical, a $-CH_2CONH_2$, $-CH_2CN$ radical, a $-(CH_2)_2NH_2$ or $-(CH_2)_2Nalk^+X^-$ radical, X being a halogen atom and alk an alkyl radical containing up to 8 carbon atoms,

Y represents a hydrogen atom, a hydroxyl, radical or a halogen atom or an $-OSO_3H$ radical or one of the salts of this radical,

W represents a hydrogen atom or an -OH radical,

Z represents a hydrogen atom or a methyl radical

as well as the addition salts with acids of the products of formula (I).

2) The compounds of formula (I) defined in claim 1 in which T represents a hydrogen atom.

3) The compounds of formula (I) defined in claim 1 or 2 in which W represents a hydrogen atom.

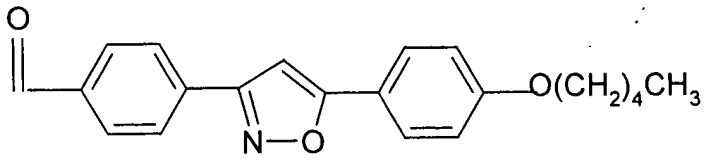
4) The compounds of formula (I) defined in any one of claims 1 to 3, in which Z represents a methyl radical.

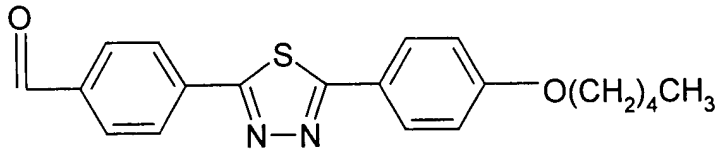
5) The compounds of formula (I) defined in any one of claims 1 to 4 in which Y represents a hydrogen atom.

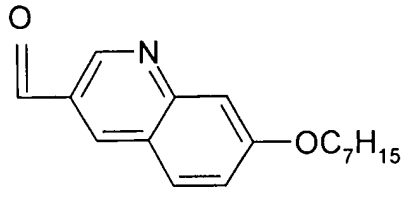
6) The compounds of formula (I) defined in any one of claims 1 to 5 in which R_3 represents a methyl radical.

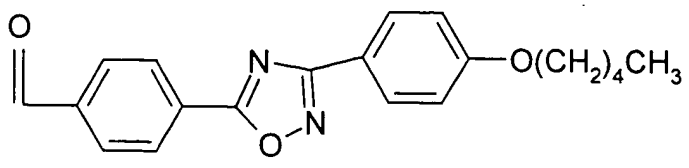
7) The compounds of formula defined in any one of claims 1 to 6, in which R_4 represents a hydroxyl radical.

8) The compounds of formula (I) defined in any one of claims 1 to 7 in which R represents a

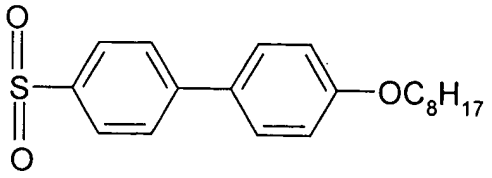








~~radical~~
~~or a~~

and 

~~radical~~.

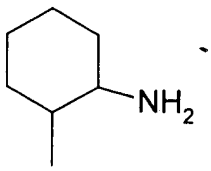
9) ~~The~~ A compounds of ~~formula I defined in any one of~~ claims 1 ~~to 8~~ in which R_1 ~~represents a~~ is hydrogen ~~radical~~.

10) ~~The~~ A compounds of ~~formula defined in any one of~~ claims 1 ~~to 9~~ in which R_2 ~~represents a~~ is

$(CH_2)_2\ NH_2$

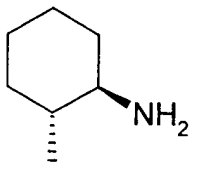
~~radical.~~

11) ~~The~~ A compounds of ~~formula I defined in any one of~~ claims 1 ~~to 9~~ in which R_2 ~~represents a~~ is

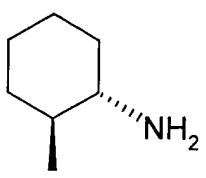


~~radical and in particular the~~

20. A compound of claim 11 wherein R_2 is

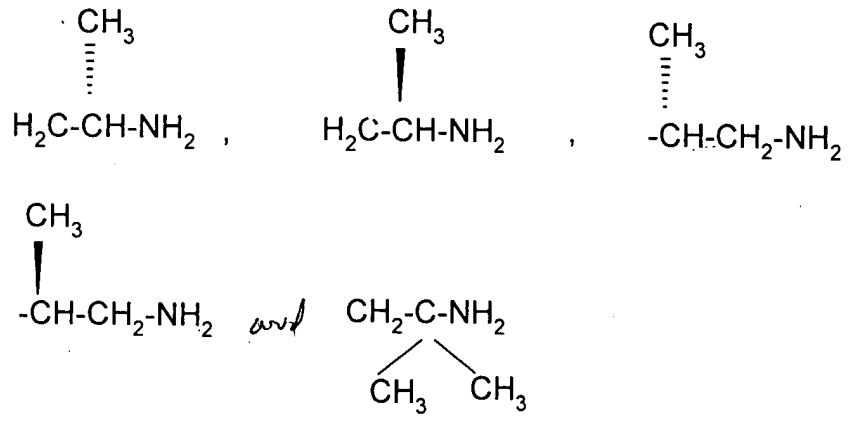


OR



~~radicals.~~

12. (~~12~~) ~~The~~ compounds of ~~formula I defined in any one of~~ claims 1 ~~to 9~~ in which R_2 ~~represents a~~ is selected from the group consisting of



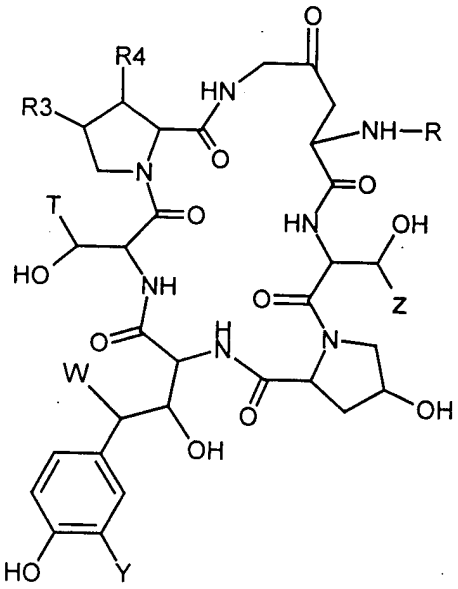
~~radical~~.

13. (~~13~~) ~~The~~ compounds of ~~formula I defined in~~ claim 1 ~~the names of which follow:~~ selected from the group consisting of

- 1-[4-[(2-aminoethyl)-amino]-N2-[[4-[5-[4-(pentyloxy)-phenyl]-3-isoxazolyl]-phenyl]-carbonyl]-L-ornithine]-4-[4-(4-hydroxyphenyl)-L-threonine]-5-L-serine-echinocandine B trifluoroacetate,
- trans-1-[4-[(2-aminocyclohexyl)-amino]-N2-[[4-[5-[4-(pentyloxy)-phenyl]-3-isoxazolyl]-phenyl]-carbonyl]-L-ornithine]-4-[4-(4-hydroxyphenyl)-L-threonine]-5-L-serine-echinocandine B trifluoroacetate,
- 1-[4-[(2(S)-aminopropyl)-amino]-N2-[[4-[5-[4-(pentyloxy)-phenyl]-3-isoxazolyl]-phenyl]-carbonyl]-L-ornithine]-4-[4-(4-hydroxyphenyl)-L-threonine]-5-L-serine-echinocandine B trifluoroacetate,
- 1-[4-[(2-aminoethyl)amino]-N2-[[4-[5-[4-(pentyloxy)-phenyl]-1,3,4-thiadiazol-2-yl]-phenyl]-carbonyl]-L-ornithine]-4-[4-(4-hydroxyphenyl)-L-threonine]-5-L-serine-echinocandine B trifluoroacetate,
- trans 1-[4-[(2-aminocyclohexyl)-amino]-N2-[[4-[5-[4-(pentyloxy)-phenyl]-1,3,4-thiadiazol-2-yl]-phenyl]-carbonyl]-L-ornithine]-4-[4-(4-hydroxyphenyl)-L-threonine]-5-L-serine-echinocandine B trifluoroacetate and
- trans 1-[4-[(2-aminocyclohexyl)-amino]-N2-[[4-[3-[4-

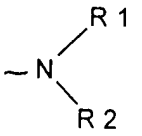
(pentyloxy)-phenyl]-1,2,4-oxadiazol-5-yl]-phenyl]-carbonyl]-L-ornithine]-4-[4-(4-hydroxyphenyl)-L-threonine]-5-L-serine-echinocandine B trifluoroacetate.

14) A process for the preparation of the compounds of formula (I) defined in any one of claims 1 to 13, characterized in that a compound of formula (II)



(II)

in which R, R_3, R_4, T, Y, W and Z retain their previous meaning, is subjected to the action of an amine or of an amine derivative capable of introducing

the  radical in which R1 and R2 retain their previous meaning and if desired to the action of a reducing agent,

and/or of a functionalization agent of the amine,

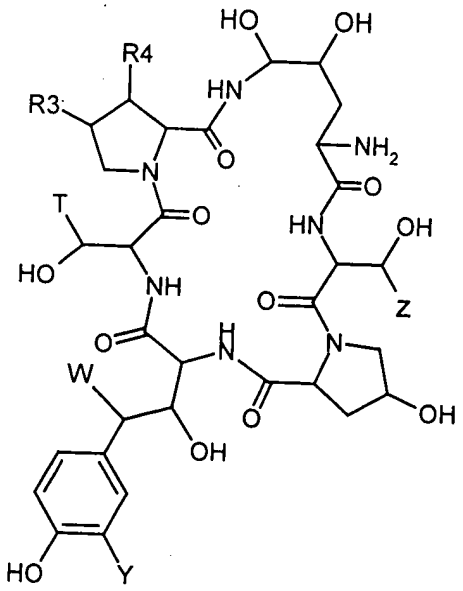
and/or of an acid in order to form the salt of the product obtained,

and/or of a separation agent of the different isomers obtained,

and in this way the compound of formula (I) as defined in claim 1 is obtained.

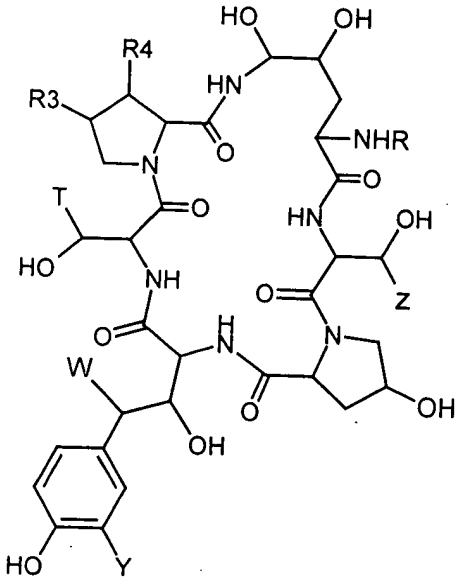
15) As new chemical products, the compounds of formula (II) wherein R_3, R_4, T, W, Y and Z are defined as in claim 14.

16) A process according to claim 14 characterized in that a compound, formula (III)



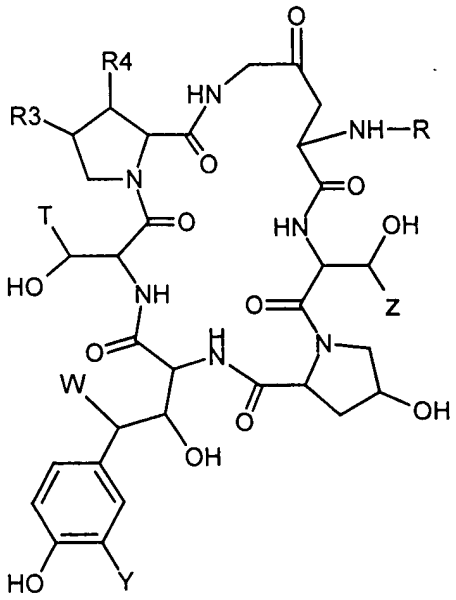
(III)

in which the different substituents retain their previous meaning is subjected to the action of an agent capable of replacing $-NH_2$ by $-NHR$, R retaining its previous meaning in order to obtain the compound of formula (IV)



(IV)

~~which is subjected to the action of~~ reacting the said compound with trimethylsilyl iodide ~~in order~~ to obtain the corresponding compound of the formula ~~(II)~~



(II)

17) As new chemical products the compounds of formula III and IV defined in claim 16.

18) As antifungal compounds, the compounds of formula (I) defined in any one of claims 1 to 13, as well as their addition salts with acids.

19) The pharmaceutical compositions containing at least one compound of formula (I) defined in any one of claims 1 to 13 as a medicament, as well as their addition salts with pharmaceutically acceptable acids.